

## WEST Search History





DATE: Thursday, February 22, 2007

Hide?	<u>Set Name</u>	<u>Query</u>	<u>Hit Count</u>
		<i>DB=PGPB,USPT,EPAB; PLUR=YES; OP=ADJ</i>	
<input type="checkbox"/>	L45	L43 and enzym\$.clm.	10
<input type="checkbox"/>	L44	L43 and enzyme.clm.	10
<input type="checkbox"/>	L43	L42 and l41	18
<input type="checkbox"/>	L42	l5.clm.	34875
<input type="checkbox"/>	L41	L40 and antibod\$.clm.	39
<input type="checkbox"/>	L40	l1 and l2	116
<input type="checkbox"/>	L39	l32 and sweatner.clm.	0
<input type="checkbox"/>	L38	l32 and sweetner.clm.	0
<input type="checkbox"/>	L37	l32 and seetner.clm.	0
<input type="checkbox"/>	L36	L35 and galactose	62
<input type="checkbox"/>	L35	L34 and antibod\$	62
<input type="checkbox"/>	L34	L32 not @py>1993	276
<input type="checkbox"/>	L33	L32 not @ay>1993	346
<input type="checkbox"/>	L32	l30 and L31	1515
<input type="checkbox"/>	L31	composition.clm.	416983
<input type="checkbox"/>	L30	galactose.clm.	3410
<input type="checkbox"/>	L29	L28 and galactose	1
<input type="checkbox"/>	L28	5632990.pn.	1
<input type="checkbox"/>	L27	L23 not @ay>1995	6
<input type="checkbox"/>	L26	L23 not @ay>1993	2
<input type="checkbox"/>	L25	L23 and L5	128
<input type="checkbox"/>	L24	L23 not @py>1993	2
<input type="checkbox"/>	L23	L22 and L21	131
<input type="checkbox"/>	L22	mannose or galactose or acetylglucosamine or acetylactose or glucose or fucose	178013
<input type="checkbox"/>	L21	L20 and CEA	158
<input type="checkbox"/>	L20	L19 and L16	1187
<input type="checkbox"/>	L19	\$glucuronidase	10866
<input type="checkbox"/>	L18	L17 and L7	3
<input type="checkbox"/>	L17	L16 not @ay>1993	3514

<input type="checkbox"/>	L16	antibod\$ NEAR2 enzyme	24424
<input type="checkbox"/>	L15	5632990.pn.	1
<input type="checkbox"/>	L14	L13 and CEA	0
<input type="checkbox"/>	L13	L12 not @py>1993	7
<input type="checkbox"/>	L12	L11 and L5	437
<input type="checkbox"/>	L11	L10 and L7	513
<input type="checkbox"/>	L10	enzyme and antibod\$	138108
<input type="checkbox"/>	L9	L8 not @ay>1993	3
<input type="checkbox"/>	L8	L7 and L6	151
<input type="checkbox"/>	L7	glucoronidase	663
<input type="checkbox"/>	L6	L5 and L4	32358
<input type="checkbox"/>	L5	conjugate or fusion	239183
<input type="checkbox"/>	L4	L3 and antibod\$	41141
<input type="checkbox"/>	L3	enzyme and L2	46628
<input type="checkbox"/>	L2	glycoprotein or glycopolypeptide	56461
<input type="checkbox"/>	L1	(bosslet or Czech or hoffman).in.	7326

END OF SEARCH HISTORY

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FILE 'HOME' ENTERED AT 11:01:16 ON 22 FEB 2007

=> file medline

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

FILE 'MEDLINE' ENTERED AT 11:01:24 ON 22 FEB 2007

FILE LAST UPDATED: 21 Feb 2007 (20070221/UP). FILE COVERS 1950 TO DATE.

All regular MEDLINE updates from November 15 to December 16 have been added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R)) and 2007 tree numbers.

The annual reload will be available in early 2007.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s antibod?

L1 733926 ANTIBOD?

=> s enzyme?

L2 805235 ENZYME?

=> s l2 and l1

L3 106352 L2 AND L1

=> s conjugat? or fusion or link? or coupl?

84773 CONJUGAT?

144879 FUSION

9402 FUSIONS

148875 FUSION

(FUSION OR FUSIONS)

442643 LINK?

180421 COUPL?

L4 808454 CONJUGAT? OR FUSION OR LINK? OR COUPL?

=> s l4 (L) l3

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH

FIELD CODE - 'AND' OPERATOR ASSUMED 'L4 (L) L3'

L5 66727 L4 (L) L3

=> s l4 and l3

L6 66727 L4 AND L3

=> s ?glururonidase

L7 1 ?GLURURONIDASE

=> s glucuronidase

14401 GLUCURONIDASE

295 GLUCURONIDASES

L8 14452 GLUCURONIDASE

(GLUCURONIDASE OR GLUCURONIDASES)

PubMed ID: 1739623

TITLE: Molecular and functional characterisation of a  
fusion protein suited for tumour specific prodrug  
activation.

AUTHOR: Bosslet K; Czech J; Lorenz P; Sedlacek H H; Schuermann M;  
Seemann G

CORPORATE SOURCE: Research Laboratory of Behringwerke, Marburg, Germany.

SOURCE: British journal of cancer, (1992 Feb) Vol. 65, No. 2, pp.  
234-8.  
Journal code: 0370635. ISSN: 0007-0920.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199203

ENTRY DATE: Entered STN: 10 Apr 1992  
Last Updated on STN: 10 Apr 1992  
Entered Medline: 24 Mar 1992

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1642BJF

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

\* \* \* \* \* Welcome to STN International \* \* \* \* \*

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America  
NEWS 2 "Ask CAS" for self-help around the clock  
NEWS 3 OCT 23 The Derwent World Patents Index suite of databases on STN  
has been enhanced and reloaded  
NEWS 4 OCT 30 CHEMLIST enhanced with new search and display field  
NEWS 5 NOV 03 JAPIO enhanced with IPC 8 features and functionality  
NEWS 6 NOV 10 CA/CAPLUS F-Term thesaurus enhanced  
NEWS 7 NOV 10 STN Express with Discover! free maintenance release Version  
8.01c now available  
NEWS 8 NOV 20 CA/CAPLUS to MARPAT accession number crossover limit increased  
to 50,000  
NEWS 9 DEC 01 CAS REGISTRY updated with new ambiguity codes  
NEWS 10 DEC 11 CAS REGISTRY chemical nomenclature enhanced  
NEWS 11 DEC 14 WPIDS/WPINDEX/WPIX manual codes updated  
NEWS 12 DEC 14 GBFULL and FRFULL enhanced with IPC 8 features and  
functionality  
NEWS 13 DEC 18 CA/CAPLUS pre-1967 chemical substance index entries enhanced  
with preparation role  
NEWS 14 DEC 18 CA/CAPLUS patent kind codes updated  
NEWS 15 DEC 18 MARPAT to CA/CAPLUS accession number crossover limit increased  
to 50,000  
NEWS 16 DEC 18 MEDLINE updated in preparation for 2007 reload  
NEWS 17 DEC 27 CA/CAPLUS enhanced with more pre-1907 records  
NEWS 18 JAN 08 CHEMLIST enhanced with New Zealand Inventory of Chemicals  
NEWS 19 JAN 16 CA/CAPLUS Company Name Thesaurus enhanced and reloaded  
NEWS 20 JAN 16 IPC version 2007.01 thesaurus available on STN  
NEWS 21 JAN 16 WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data  
NEWS 22 JAN 22 CA/CAPLUS updated with revised CAS roles  
NEWS 23 JAN 22 CA/CAPLUS enhanced with patent applications from India  
NEWS 24 JAN 29 PHAR reloaded with new search and display fields  
NEWS 25 JAN 29 CAS Registry Number crossover limit increased to 300,000 in  
multiple databases  
NEWS 26 FEB 13 CASREACT coverage to be extended  
NEWS 27 Feb 15 PATDPASPC enhanced with Drug Approval numbers  
NEWS 28 Feb 15 RUSSIAPAT enhanced with pre-1994 records

NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT  
MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),  
AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

NEWS HOURS STN Operating Hours Plus Help Desk Availability  
NEWS LOGIN Welcome Banner and News Items  
NEWS IPC8 For general information regarding STN implementation of IPC 8  
NEWS X25 X.25 communication option no longer available

Enter NEWS followed by the item number or name to see news on that  
specific topic.

=> s ?glucuronidase  
L9 14419 ?GLUCURONIDASE

=> s l9 and l6  
L10 97 L9 AND L6

=> s CEA or (Carcinogenic Embryonic Antigen)  
11451 CEA  
376 CEAS  
11479 CEA  
(CEA OR CEAS)  
19461 CARCINOGENIC  
6 CARCINOGENICS  
19466 CARCINOGENIC  
(CARCINOGENIC OR CARCINOGENICS)  
100070 EMBRYONIC  
6 EMBRYONICS  
100072 EMBRYONIC  
(EMBRYONIC OR EMBRYONICS)  
372385 ANTIGEN  
450906 ANTIGENS  
633561 ANTIGEN  
(ANTIGEN OR ANTIGENS)  
2 CARCINOGENIC EMBRYONIC ANTIGEN  
(CARCINOGENIC(W) EMBRYONIC(W) ANTIGEN)  
L11 11481 CEA OR (CARCINOGENIC EMBRYONIC ANTIGEN)

=> s l11 and l10  
L12 2 L11 AND L10

=> d ibib 1-2

L12 ANSWER 1 OF 2 MEDLINE on STN  
ACCESSION NUMBER: 1998404122 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9733483  
TITLE: Prodrugs of anthracyclines for use in antibody  
-directed enzyme prodrug therapy.  
AUTHOR: Florent J C; Dong X; Gaudel G; Mitaku S; Monneret C; Gesson  
J P; Jacquesy J C; Mondon M; Renoux B; Andrianomenjanahary  
S; Michel S; Koch M; Tilleguin F; Gerken M; Czech J; Straub  
R; Bosslet K  
CORPORATE SOURCE: UMR 176 CNRS/Institut Curie, Section Recherche, 26 rue  
d'Ulm, F-75248 Paris Cedex 05, France.  
SOURCE: Journal of medicinal chemistry, (1998 Sep 10) Vol. 41, No.  
19, pp. 3572-81.  
Journal code: 9716531. ISSN: 0022-2623.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199810  
ENTRY DATE: Entered STN: 20 Oct 1998  
Last Updated on STN: 20 Oct 1998  
Entered Medline: 8 Oct 1998

L12 ANSWER 2 OF 2 MEDLINE on STN  
ACCESSION NUMBER: 92153684 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 1739623  
TITLE: Molecular and functional characterisation of a  
fusion protein suited for tumour specific prodrug  
activation.  
AUTHOR: Bosslet K; Czech J; Lorenz P; Sedlacek H H; Schuermann M;  
Seemann G  
CORPORATE SOURCE: Research Laboratory of Behringwerke, Marburg, Germany.

SOURCE: British journal of cancer, (1992 Feb) Vol. 65, No. 2, pp. 234-8.  
Journal code: 0370635. ISSN: 0007-0920.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199203  
ENTRY DATE: Entered STN: 10 Apr 1992  
Last Updated on STN: 10 Apr 1992  
Entered Medline: 24 Mar 1992

=> d ibib abs 2

L12 ANSWER 2 OF 2 MEDLINE on STN  
ACCESSION NUMBER: 92153684 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 1739623  
TITLE: Molecular and functional characterisation of a fusion protein suited for tumour specific prodrug activation.  
AUTHOR: Bosslet K; Czech J; Lorenz P; Sedlacek H H; Schuermann M; Seemann G  
CORPORATE SOURCE: Research Laboratory of Behringwerke, Marburg, Germany.  
SOURCE: British journal of cancer, (1992 Feb) Vol. 65, No. 2, pp. 234-8.  
Journal code: 0370635. ISSN: 0007-0920.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199203  
ENTRY DATE: Entered STN: 10 Apr 1992  
Last Updated on STN: 10 Apr 1992  
Entered Medline: 24 Mar 1992

AB A fusion protein consisting of the humanised Fab fragment of the anti CEA MAb BW 431 and the human beta-glucuronidase was expressed in BHK cells. Functional testing revealed that the specificity and avidity of the humanised V region was similar to the original murine MAb BW 431. Furthermore, the enzymatic activity, pH sensitivity and stability of the human beta-glucuronidase in the fusion protein was comparable to the activity of recombinant human beta-glucuronidase. Using anti-idiotypic affinity chromatography, two molecules of a molecular weight of 125 kDa or 250 kDa could be visualized under nonreducing conditions in SDS-PAGE. Reducing conditions revealed a 25 kDa light and 100 kDa heavy chain. Due to its suitable biological characteristics this fusion protein might be an appropriate molecule allowing a site specific antibody directed enzyme prodrug therapy (ADEPT) in vivo.

=> d his

(FILE 'HOME' ENTERED AT 11:01:16 ON 22 FEB 2007)

FILE 'MEDLINE' ENTERED AT 11:01:24 ON 22 FEB 2007

L1 733926 S ANTIBOD?  
L2 805235 S ENZYME?  
L3 106352 S L2 AND L1  
L4 808454 S CONJUGAT? OR FUSION OR LINK? OR COUPL?  
L5 66727 S L4 (L) L3  
L6 66727 S L4 AND L3  
L7 1 S ?GLURURONIDASE  
L8 14452 S GLUCURONIDASE

L9 14419 S ?GLUCURONIDASE  
L10 97 S L9 AND L6  
L11 11481 S CEA OR (CARCINOGENIC EMBRYONIC ANTIGEN)  
L12 2 S L11 AND L10

=> s 13 and 19  
L13 304 L3 AND L9

=> s 113 and 111  
L14 2 L13 AND L11

=> file pctfull	SINCE FILE	TOTAL
COST IN U.S. DOLLARS	ENTRY	SESSION
FULL ESTIMATED COST	3.68	3.89

FILE 'PCTFULL' ENTERED AT 11:05:55 ON 22 FEB 2007  
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FILE LAST UPDATED: 20 FEB 2007 <20070220/UP>  
MOST RECENT UPDATE WEEK: 200707 <200707/EW>  
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

=> s antibod?  
L15 95616 ANTIBOD?

=> s ?glucuronidase  
L16 6166 ?GLUCURONIDASE

=> s enzyme?  
L17 135831 ENZYME?

=> s 115 (4W) 117  
L18 11277 L15 (4W) L17

=> s conjugat? or fusion or link? or coupl?  
82444 CONJUGAT?  
84421 FUSION  
16216 FUSIONS  
85622 FUSION  
(FUSION OR FUSIONS)  
327777 LINK?  
363802 COUPL?  
L19 576301 CONJUGAT? OR FUSION OR LINK? OR COUPL?

=> s 119 and 118  
L20 10996 L19 AND L18

=> s 120 and 116  
L21 1160 L20 AND L16

=> s CEA or (Carcinogenic Embryonic Antigen)  
4397 CEA  
83 CEAS  
4455 CEA  
(CEA OR CEAS)  
4047 CARCINOGENIC  
115 CARCINOGENICS  
4157 CARCINOGENIC  
(CARCINOGENIC OR CARCINOGENICS)  
23813 EMBRYONIC  
2 EMBRYONICS



23814 EMBRYONIC  
 (EMBRYONIC OR EMBRYONICS)  
 59847 ANTIGEN  
 40235 ANTIGENS  
 65876 ANTIGEN  
 (ANTIGEN OR ANTIGENS)  
 18 CARCINOGENIC EMBRYONIC ANTIGEN  
 (CARCINOGENIC(W) EMBRYONIC(W) ANTIGEN)  
 L22 4458 CEA OR (CARCINOGENIC EMBRYONIC ANTIGEN)

=> s 122 and 121  
 L23 80 L22 AND L21

=> s 123 and galactose  
 16533 GALACTOSE  
 191 GALACTOSES  
 16548 GALACTOSE  
 (GALACTOSE OR GALACTOSES)  
 L24 28 L23 AND GALACTOSE

=> s 124 not py>1993  
 1073184 PY>1993  
 L25 2 L24 NOT PY>1993

=> d ibib 1-2

L25 ANSWER 1 OF 2 PCTFULL COPYRIGHT 2007 Univentio on STN  
 ACCESSION NUMBER: 1993002703 PCTFULL ED 20020513  
 TITLE (ENGLISH): PRODRUGS ACTIVATED BY TARGETED CATALYTIC PROTEINS  
 TITLE (FRENCH): PROMEDICAMENTS ACTIVES PAR DES PROTEINES CATALYTIQUES  
 CIBLEES  
 INVENTOR(S): KENTEN, John, Henry;  
 VON BORSTEL, Reid;  
 CASADEI, Jan, M.;  
 KAMIREDDY, Balreddy;  
 MARTIN, Mark, T.;  
 MASSEY, Richard, J.;  
 NAPPER, Andrew, D.;  
 SIMPSON, David, M.;  
 SMITH, Rodger, G.;  
 TITMAS, Richard, C.;  
 WILLIAMS, Richard, O.  
 PATENT ASSIGNEE(S): IGEN, INC.  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9302703	A1	19930218
DESIGNATED STATES			
W:	AU CA JP KR AT BE CH DE DK ES FR GB GR IE IT LU MC NL		
	SE		
PRIORITY INFO.:	US 1991-740,501		19910805
	US 1991-773,042		19911010
	US 1992-919,851		19920731
APPLICATION INFO.:	WO 1992-US6530	A	19920804

L25 ANSWER 2 OF 2 PCTFULL COPYRIGHT 2007 Univentio on STN  
 ACCESSION NUMBER: 1979000882 PCTFULL ED 20020506  
 TITLE (ENGLISH): MACROMOLECULAR ENVIRONMENT CONTROL IN SPECIFIC RECEPTOR  
 ASSAYS  
 TITLE (FRENCH): CONTROLE D'UN MILIEU MACROMOLECULAIRE DANS DES  
 RECEPTEURS D'ESSAI SPECIFIQUES  
 INVENTOR(S): LITMAN D;

PATENT ASSIGNEE(S):  
LANGUAGE OF PUBL.:  
DOCUMENT TYPE:  
PATENT INFORMATION:

WIFE R;  
ULLMAN E;  
HAREL Z;  
MAGGIO E  
SYVA CO  
English  
Patent

NUMBER	KIND	DATE
WO 7900882	A1	19791101

DESIGNATED STATES

W: BR JP SE CH DE FR GB  
PRIORITY INFO.: US 1978-893650 19780405  
US 1978-964099 19781124  
APPLICATION INFO.: WO 1979-US202 A 19790402

=> d ibib abs kwic

L25 ANSWER 1 OF 2 PCTFULL COPYRIGHT 2007 Univentio on STN  
ACCESSION NUMBER: 1993002703 PCTFULL ED 20020513  
TITLE (ENGLISH): PRODRUGS ACTIVATED BY TARGETED CATALYTIC PROTEINS  
TITLE (FRENCH): PROMEDICAMENTS ACTIVES PAR DES PROTEINES CATALYTIQUES CIBLEES

INVENTOR(S): KENTEN, John, Henry;  
VON BORSTEL, Reid;  
CASADEI, Jan, M.;  
KAMIREDDY, Balreddy;  
MARTIN, Mark, T.;  
MASSEY, Richard, J.;  
NAPPER, Andrew, D.;  
SIMPSON, David, M.;  
SMITH, Rodger, G.;  
TITMAS, Richard, C.;  
WILLIAMS, Richard, O.

PATENT ASSIGNEE(S): IGEN, INC.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9302703	A1	19930218

DESIGNATED STATES

W: AU CA JP KR AT BE CH DE DK ES FR GB GR IE IT LU MC NL  
SE  
PRIORITY INFO.: US 1991-740,501 19910805  
US 1991-773,042 19911010  
US 1992-919,851 19920731  
APPLICATION INFO.: WO 1992-US6530 A 19920804

ABEN Disclosed and claimed are prodrugs activated by catalytic proteins, such as enzymes and catalytic antibodies. The invention comprehends such prodrugs, as well as haptens, to elicit catalytic antibodies to activate the prodrugs. The prodrugs are useful as cytotoxic chemotherapeutic agents, e.g., as antitumor agents.

ABFR L'invention concerne des promedicaments actives par des proteines catalytiques telles que des enzymes et des anticorps catalytiques. L'invention concerne lesdits promedicaments, ainsi que des haptenes destines a induire les anticorps catalytiques a activer les promedicaments. Lesdits promedicaments sont utiles comme agents chimiotherapeutiques

cytotoxiques par exemple comme agents  
antitumoraux.

DETD . . . Senter, et al., Patent Application EP 88112646,  
similarly suggest the use of fluorouridine monophosphate to be activated  
by the enzyme  
alkaline phosphatase conjugated to an antibody that binds to a  
tumor cell surface antigen.

.  
in fact more  
than 100 fold less toxic than melphelan to particular cell lines in  
culture, pretreatment of cells  
with an antibody-PVA conjugate failed to enhance the toxicity  
of the prodrug because PVA  
hydrolyzed the phenoxyacetamide bond of the prodrug too slowly to  
generate. . .

#### Catalytic Proteins

a. E

.n=es

The prior art discloses the use of non-mammalian enzymes  
conjugated to targeting antibodies  
in order to activate the prodrug selectively at tumor sites (e.g.,  
carboxypeptidases described in  
Bagshawe, et al., Patent Application. . .

.  
are administered;  
neuraminidase removes the sialic acid residue at the terminus of  
oligosaccharides on  
glycoproteins (important components of erythrocyte membranes, for  
example), exposing  
galactose residues which mark such glycoproteins for rapid  
degradation in the liver. Due  
consideration of the situation in vivo is necessary for. . .

.  
whose electrostatic and  
shape characteristics can be mimicked by a phosphonate structure.  
Immunization of a mouse  
with a nitrophenyl phosphonate ester hapten-protein conjugate  
led to the isolation of  
monoclonal antibodies with hydrolytic activity on methyl-p-nitrophenyl  
carbonate (Jacobs, et  
al., J. Am. Chem. Soc. 109 (1987):2174-2176).. . .

.  
could cleave an aryl carboxamide (Janda, et  
al., Science 241 (1988):1188-1191). Another scheme for production of  
peptidases utilized a  
metal complex cofactor linked to a peptide (Iverson, et al.,  
Science 243 (1989):1184-1188).

The term moiety as used herein with reference to immunoconjugates means  
the whole

antibody, enzyme or targeting protein, or active  
fragment thereof.

(i) a moiety capable of binding to an epitope of a specific cell  
population, and

(ii) a catalytic antibody moiety or enzyme moiety  
capable of activating said novel  
prodrug of the subject invention.

(i) a moiety capable of binding to an epitope of a specific cell  
population, and

(H) a catalytic antibody moiety or enzyme moiety

capable, of activating a novel  
prodrug of the subject invention;  
(b) permitting said immunoconjugate to become localized at said cell  
population; . . .

2;

VL antibody I-S-VH antibody 1-S-VL antibody 2-S-VH antibody 2;  
VL antibody I-S-VH antibody I-S-VH antibody 2-S-VL antibody 2;  
wherein -S- is a linker sequence; and  
(ii) isolating said bispecific antibody.

1-S-VL antibody 2,

(iii) combining the products of steps (i) and (ii), and

9 I

(iv) isolating said bispecific antibody,  
wherein -S- is a linker sequence.

antibody 2-S-VL antibody 1,

(M) combining the products of steps (i) and (ii), and

(iv) isolating said bispecific antibody,  
wherein -S- is a linker sequence.

Figure 11 (Sheet 31/87) shows the site specific activation of  
galactosyl-AraC prodrug  
on CEA antigen positive cells.

Figure 12 (Sheet 32/87) shows the activity of galactosyl-AraC prodrug on  
CEA antigen  
negative cells.

Figure 18 (Sheet 38/87) shows the comparison of 5' fluorouridine and  
galactosyl-5'  
fluorouridine prodrug on CEA antigen negative Colo cells.

Figure 19 (Sheet 39/87) shows the site specific activation of  
Tfluorouridine prodrug  
on CEA antigen positive Lovo cells.

Figure 20 (Sheet 40/87) shows the, activity of 5'Ruorouridine prodrug on  
CEA antigen  
negative Colo cells.

in or near tumors by prior administration of tumor-selective  
agents such as receptor-binding ligands, analogs which bind to tumor  
associated enzymes,  
and antibodies conjugated to or otherwise physically connected  
to a protein catalyst  
which converts the prodrugs to active cytotoxic agents. The catalytic  
protein is. . .

Catalytic antibodies, as well as enzymes, catalyze  
chemical reactions by lowering the  
activation energy required to form the short-lived, unstable transition  
state. Catalytic  
antibodies which] stabilize or enhance. . .

used as haptens for eliciting antibodies with catalytic  
activity toward prodrugs of the invention. As such, their structure  
generally includes a linker  
arm for attachment to a protein carrier. Thus, the moiety of the hapten  
corresponding to the  
drug in the prodrug is typically an analog of the original drug,  
differing in the presence of a  
covalently-attached linker arm terminating in a group can be

attached to a prote . In  
some embodiments of the invention, the linker arm is attached  
to the moiety of the hapten  
corresponding to the prodrug substituent (e.g., the substituted benzoate  
portion of an. . .

The catalytic proteins of the invention are conjugated to, or  
otherwise physically associated  
with, a tumor-selective antibody, antibody fragment, or binding protein  
or analogs to tumor-  
associated proteins or tumor-selective. . .

hydrolyzes acetals (or ortho esters) to aldehydes (or acids)  
D. Glycosidase - cleaves sugar substituents attached to drugs via a  
glycoside linkage.

Hexopyranose conjugated to drug hydroxyl group via the  
anomeric position of the  
sugar.

2. Hexofuranose conjugated to drug hydroxyl group via the  
anomeric position of the  
sugar.

in the structure of X. Typically, however, X' will be very similar to X,  
generally  
differing in that X' contains a linker arm for joining the  
transition-state analog to a carrier  
protein such as bovine serum albumin (BSA) or keyhole limpet hemocyanin  
(KLH). . .

R2'

R3 R

RV

wherein X is an analog of X of compound AI a, and Y is optionally  
linked to a  
carrier protein,

B is O, S, NH, or CH<sub>2</sub>,

D is P(O)OH, SO<sub>2</sub>, CHOH or SO (with any stereochemistry), if D is CHOH  
then B

is CH<sub>2</sub>, and

R1', R2', R3', R4' and RY are the same or different, are optionally  
linked to a carrier

protein and are H, alkyl with 1 - 10 carbon atoms, alkoxy with 1 - 10.

R6'

RT

R8' D's]B0000 X

wherein X is an analog of X of compound A2a, and X' is optionally  
linked to carrier  
protein,

B is O, S, NH, or CH<sub>2</sub>,

D' is P(O), COH (with any stereochemistry), if D' is COH then B and Y are.

. . . ester groups, ether groups, -CO-,

cyano, epoxide groups and heteroatoms,

R6', R7', R8', and R9' are the same or different, are optionally

linked to the carrier

protein and are H, alkyl with 1 - 10 carbon atoms, alkoxy with 1 - 10.

R10'

R11'

R12

wherein Y is an analog of X of Ma, and Y is optionally linked to carrier protein,  
B is O, S, NH, or CH<sub>2</sub>.

D is P(O)OH, SO<sub>2</sub>, CHOH or SO with any stereochemistry, if D is CHOH then B is CH<sub>2</sub>, and  
R<sup>10'</sup>-R<sup>12'</sup> which are optionally linked to the carrier protein, are the same or different but at least two of them are not H, and are H. . .

6.]\_ Y

I

D' x

R<sup>13</sup>

4

wherein X' is an analog of compound Ma, and X' is optionally linked to a carrier protein,

B is O, S, NH, or CH<sub>2</sub>,

D' is P(O), COH with any stereochemistry, if D' is COH, then B and. . .

R<sup>16'</sup>

R<sup>17</sup> R<sup>15'</sup>

R<sup>18</sup> a\*,

wherein X' is an analog of X of compound B 1 a, and X' is optionally linked to the

carrier protein,

B is O, S, NH, or CH<sub>2</sub>,

D is P(O)OH, SO<sub>2</sub>, CHOH or SO with any stereochemistry, if D is CHOH then

B is

CH<sub>2</sub>, and

R<sup>15'</sup>, R<sup>16'</sup>, R<sup>17</sup> R<sup>18'</sup> and R<sup>19'</sup> are the same or different, are optionally linked to the

carrier protein, and are H, alkyl with 1-10 carbon atoms, alkoxy with 1-10 carbon atoms,

monocyclic aromatic, alkene with 1-10. . .

R<sup>20'</sup>

R<sup>21</sup>

X

R<sup>22</sup> D%, B<sup>000e</sup>

wherein X is an analog of the drug XNH<sub>2</sub> of compound B<sub>2a</sub>, and X is optionally

linked to a carrier protein,

B is O, S, NH, or CH<sub>2</sub>,

D' is P(O), COH with any stereochemistry, if D' is COH then B. . .

substituents that are phenyl, alkyl, or alkyl with heteroatoms, and;

R<sup>20</sup> R<sup>21'</sup>.) R<sup>22'</sup> and R<sup>23'</sup> are the same or different, are optionally linked to the carrier

protein and are H, alkyl with 1-10 carbon atoms, alkoxy with 1-10 carbon atoms, monocyclic

aromatic, alkene with 1-10. . .

wherein X is an analog of X of compound B<sub>3a</sub>, and X' is optionally linked to the

carrier protein,

B is O, S, NH, or CH<sub>2</sub>, and

D is HP(O)OH, CH<sub>2</sub>OH, P(O)(OH)<sub>2</sub>, or SO<sub>3</sub>H, if D is CH<sub>2</sub>OH. . .

R<sup>24'</sup>

R<sup>25'</sup> ell]x

R

wherein X is an analog of X of compound B4a, and X is optionally linked to the carrier protein,  
B is O, S, NH, or CH<sub>2</sub>,  
D is P(O)OH, SO<sub>2</sub>, CHOH or SO with any stereochemistry, if D is CHOH then B is CH<sub>2</sub>, and  
R<sub>24'</sub>-R<sub>26'</sub> which are optionally linked to a carrier protein, are the same or different and are H, alkyl with 2 to 22 carbon atoms, alkyl with. . .

J Y

R<sub>27</sub> \*]4%B000e

wherein X' is an analog of X of compound B5a, and X' is optionally linked to the carrier protein,  
B is O, S, NH, or CH<sub>2</sub>,  
D' is P(O), COH with any stereochemistry, if D' is COH then B and. . . heteroatoms with 1-9 atoms in a linear configuration which have substituents that are phenyl, alkyl, or alkyl with heteroatoms, and  
R<sub>27</sub>-R<sub>28'</sub> which are optionally linked to the carrier protein are the same or different and are H, alkyl with 2 to 22 carbon atoms, alkyl with. . .

In all strategies, the structure of the substituents will depend on the drug (occupying R)

conjugation to an immunogenic carrier protein including but not limited to KLH or BSA (through R, R', or R) and the structure. . .

at least one of R<sub>30'</sub> and R<sub>3</sub> F is an analog of X of compound B6a, and said analog is optionally linked to a carrier protein,  
D . . . is SO<sub>2</sub>, SO or CHOH with any stereochemistry, if D . . . is CHOH then E is CH,  
Z is. . . heterocyclic or phenyl substitution (optionally substituted on the heterocyclic or phenyl group), and  
R<sub>29'</sub> is optionally SO<sub>3</sub>H or SO<sub>4</sub>H, and  
R<sub>29v</sub> -3T are optionally linked to a carrier protein.

R O

Fi<sub>36'</sub> 00000 X

B

R<sub>351</sub> 2)n

Al

wherein X' is an analog of X of compound B6c, and is optionally linked to carrier protein,

B is O, S, NH, or CH<sub>2</sub>,

R<sub>34</sub>]1 R<sub>35</sub>% R<sub>36'</sub>. and R<sub>37'</sub> are the same or different and are H,. . .

O

(CH<sub>2</sub>)<sub>n</sub> 000

k-]E' B

F<sub>14</sub>,V

wherein X' is an analog of X of compound B6e, and X is optionally linked to carrier protein,

B is O, S, NH, or CH<sub>2</sub>,

n is an interger from 0 to 4,

R<sub>43'</sub> and R<sub>44'</sub> are the same. . .

Q'] X

wherein Q' is O, S, NH, or CH<sub>2</sub>,

X is an analog of X of compound Cl a, and X is optionally linked to a carrier

protein,

B' is NE or CH<sub>2</sub>, if B' is NH, then Q' is CH<sub>2</sub>, and

R45' and R46' are the same or different and are H, alkyl unsubstituted, alkyl

substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate,

alkylammonium, alkene, or monocyclic aromatic, and are optionally linked to a carrier

protein.

different and are H, alkyl unsubstituted, alkyl

substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate,

alkylammonium, alkene, or monocyclic aromatic, and are optionally linked to a carrier

protein.

Q' is O, S, NH, or CH<sub>2</sub>,

wherein X' is an analog of X of compound Cl a, and X' is optionally linked to a

carrier protein, and

R45' and R46' are the same or different and are H, alkyl unsubstituted, alkyl

substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate,

alkylammonium, alkene, or monocyclic aromatic, and are optionally linked to a carrier

protein.

different and are H, alkyl unsubstituted, alkyl

substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate,

alkylammonium, alkene, or monocyclic aromatic, and are optionally linked to a carrier

protein.

R45 is H, aminocarboxy, alkyl unsubstituted, alkyl substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate,

alkylammonium, alkene or

monocyclic aromatic, and are optionally linked to a carrier protein.

When E which is linked to R45, is N, it is preferred that the

E-R45, linkage forms an

amide substituted with an amine moiety.

47

R -NH

wherein X' is an analog of X of compound C2a, and which is optionally linked to a

carrier protein,

Q' is O, CH<sub>2</sub>, S, or NH, and

R47' and R48' are the same or different and are H, alkyl unsubstituted, alkyl

substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate,

alkylammonium, alkene, or monocyclic aromatic, and are optionally linked to a carrier

protein.



different and are H, alkyl unsubstituted, alkyl substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic, and are optionally linked to a carrier protein.

47

NH

wherein X' is an analog of X of compound C2a, and which is optionally linked to a carrier protein, Q' is CH<sub>2</sub>, and R47' and R48' are the same or different and are H, alkyl unsubstituted, alkyl substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic, and are optionally linked to a carrier protein.

different and are H, alkyl unsubstituted, alkyl substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic, and are optionally linked to a carrier protein.

with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl ester or alkyl amide, hydroxyl, alkylammonium, or alkene, or monocyclic aromatic, and are optionally linked to a carrier protein.

RSD'

- B1

Rs' NH

wherein Q' is O, S, NH or CH<sub>2</sub>,

Y is an analog of X of compound C3a, and X is optionally linked to a carrier protein,

B' is NH or CH<sub>2</sub>, if Bis NH, then Q' is CH<sub>2</sub>, and

R50' and R51' are the same or different. . . with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl ester or alkyl amide, hydroxyl, alkylammonium, amino, alkene, or monocyclic aromatic, and are optionally linked to a carrier protein.

R50'

R51' x

wherein Q' is O, S, NH or CH<sub>2</sub>,

X' is an analog of X of compound C3a, and X' is optionally linked to a carrier protein, and

R50' and R51' are the same or different and are H, alkyl unsubstituted, alkyl

substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl ester or alkyl amide, hydroxyl, alkylammonium, amine, or monocyclic aromatic, and are optionally linked to a carrier protein.

with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl

ester or  
alkyl amide, hydroxyl, alkylammonium, amino, alkene, or monocyclic  
aromatic, and are  
optionally linked to a carrier protein.

a, - X

wherein Q' is O, S, NH or CH<sub>2</sub>,

X' is an analog of X of compound Of, and X is optionally linked  
to a carrier  
protein,

W is NH or CH<sub>2</sub>, if B' is NH, then Q' is CH<sub>2</sub>, and

G' is a radical of the diol G(OH)<sub>2</sub>, . . . cycloalkyldiol or ortho-  
phenyldiol, and G' is optionally substituted with halogens, heteroatoms,  
phosphonate,

sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic,  
and is optionally

linked to a carrier protein.

cycloalkyldiol or ortho-

phenyldiol, and G' is optionally substituted with halogens, heteroatoms,  
phosphonate,

sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic,  
and is optionally

linked to a carrier protein.

QI]X

wherein Q' is O, S, NH or CH<sub>2</sub>,

X' is an analog of X of compound Of, which is optionally linked  
to a carrier protein,  
and

G' is a radical of the diol G(OH)<sub>2</sub>, G(OH)<sub>2</sub> is a sugar, cycloalkyldiol or  
ortho-

phenyldiol, and G' is optionally substituted with halogens, heteroatoms,  
phosphonate,

sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic,  
and are optionally

linked to a carrier protein.

cycloalkyldiol or ortho-

phenyldiol, and GI is optionally substituted with halogens, heteroatoms,  
phosphonate,

sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic,  
and are optionally

linked to a carrier protein.

with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl  
ester or alkyl amide, hydroxyl, alkylammonium, amino, alkene, or  
monocyclic aromatic, and  
are optionally linked to a carrier protein.

R52 t

X

NH

wherein X' is an analog of X of compound C4a, and which is optionally  
linked to a

carrier protein,

Q' is CH<sub>2</sub> or NH, and

R52T and R53I are the same or different, and are H, alkyl unsubstituted,  
alkyl

substituted. . . with halogens, heteroatoms, phosphonate, sulfonate,  
carboxylate or alkyl ester or

alkyl amide, hydroxyl, alkylammonium, amino, alkene, or monocyclic  
aromatic, and are

optionally linked to a carrier protein.

with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl ester or alkyl amide, hydroxyl, alkylammonium, amino, alkene, or monocyclic aromatic, and are optionally linked to a carrier protein.

W

Q1- X

R NH

wherein X is an analog of X of compound C4a, and which is optionally linked to a carrier protein,

Q is CH<sub>2</sub>, and

R52' and R53' are the same or different, and are H, alkyl unsubstituted, alkyl

substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl ester or

alkyl amide, hydroxyl, alkylammonium, amino, alkene, or monocyclic aromatic, and are

optionally linked to a carrier protein.

a, - X

N

wherein Y is an analog of X of compound C4, and which is optionally linked to a carrier protein,

Q' is CH<sub>2</sub> or NH, and

G' is a radical of the diol G(OH)<sub>2</sub>, G(OH)<sub>2</sub> is a sugar, cycloalkyldiol or ortho-

phenyldiol, and G' is optionally substituted with halogens, heteroatoms, phosphonate,

sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic, and is optionally

linked to a carrier protein.

cycloalkyldiol or ortho-

phenyldiol, and G' is optionally substituted with halogens, heteroatoms, phosphonate,

sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic, and is optionally

linked to a carrier protein, and

R59' is H, alkyl unsubstituted, alkyl substituted with halogens, heteroatoms,

phosphonate, sulfonate, carboxylate or alkyl ester or alkyl amide, hydroxyl, alkylammonium,

amino, alkene, or monocyclic aromatic, and is optionally linked to a carrier protein.

G] Qv] )C

NH

wherein X is an analog of X of compound C4, and which is optionally linked to a carrier protein,

Q' is CH<sub>2</sub>, and

G' is a radical of the diol G(OH)<sub>2</sub>, G(OH)<sub>2</sub> is a sugar, cycloalkyldiol or ortho-

phenyldiol, and G' is optionally substituted with halogens, heteroatoms, phosphonate,

sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic, and is optionally

linked to a carrier protein.

cycloalkyldiol or ortho-

phenyldiol, and GI is optionally substituted with halogens, heteroatoms,

phosphonate,  
sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic,  
and is optionally  
linked to a carrier protein.

the  
nucleotide analog, in particular such prodrugs wherein said hexopyranose  
or hexofuranose is  
selected from the group consisting of glucose, glucosamine,  
D-quinovopyranose, galactose,  
galactosamine, L-fucopyranose, L-rhamnopyranose, D-glucopyranuronic  
acid, D-  
galactopyranuronic acid, D-mannopyranuronic acid, or D-iodopyranuronic  
acid.

a monosaccharide hexopyranose  
or hexofuranose which is a structural analog of a sugar selected from  
the group consisting of  
glucose, glucosamine, D-quinovopyranose, galactose,  
galactosamine, L-galactopyranuronic  
acid, D-mannopyranuronic acid, or D-iodopyranuronic acid.

A novel coupling reaction to make P-glycosylated nucleosides  
of the invention from  
hexopyranoses and nucleosides is the direct reaction of the  
peracetylated hexoses and.

The coupling reaction can be accomplished also by activation  
of the anomeric position by  
conversion to SPh, F or imidate groups and subsequent.

OH CH<sub>2</sub>OH H  
Glucosan-dne H OH H OH H NH<sub>2</sub> CH<sub>2</sub>OH H  
D - Quinovopyranose H OH H OH H OH CH<sub>3</sub> H  
Galactose OH H H OH H OH CH<sub>2</sub>OH H  
Galactosan-dne OH H H OH H NH<sub>2</sub> CH<sub>2</sub>OH H  
L-Fucopyranose OH H H OH  
L- . . . manopyranuronic acid H OH H OH OH H COOH H  
Iodopyranuronic acid H OH H OH H OH H COOH

The coupling reaction of hexofuranoses at their anomeric  
position to the nucleoside 5'  
position to make furanosylated nucleosides can be accomplished by the.

Coupling of hexofuranoses to nucleosides will make a mixture  
of anomers, because of the  
ring size.

#### D. Prodrugs Activation By Glycosidase Reaction

1 . Hexopyranose conjugated to drug hydroxyl group via the  
anomeric  
position of the sugar  
2 . Hexofuranose conjugated to drug hydroxyl group via the  
anomeric  
position of the sugar.

Q is O or NH, and  
V is a hexopyranose or hexofuranose conjugated to QX via the  
anomeric position of  
the sugar with optional alpha or beta configuration.

Advantageously V is Glucose, Glucosamine, D-Quinovopyranose,  
Galactose,  
Galactosamine, L-Fucopyranose, L- Rhamnopyranose, D-Glucopyranuronic

acid, D-  
Galactopyranuronic acid, D-manopyranuronic acid, or D-Iodopyranuronic acid.

The synthesis of the haptens is accomplished by the coupling reaction of the appropriate lactam and the corresponding 5 amino nucleoside in the presence of triethyloxonium tetrafluoroborate in methylene chloride as the. . .

A hapten (amidine TS analog) for galactose or equivalent sugar for the cleavage of the glycosidic bond to liberate drug, said hapten having the formula.

N  
I \\Q1]x  
M, le  
wherein X' is an analog of X of compound DIa, and which is optionally linked to a carrier protein,  
Q' is NH, and  
M' is a 1,4-diradical of a n-pentane where C1, C2, C3 and C5 are optionally substituted with OH, and M is optionally linked to a carrier protein.

NH  
ml  
M' is a 1,4-diradical of a n-pentane where C1, C2, C3 and C5 are optionally substituted with OH, and M' is optionally linked to a carrier protein.

NH  
M Qv] X  
wherein X' is an analog of X of compound DI a, and which is optionally linked to a carrier protein,  
Q' is CH2, and  
M' is a 1,4-diradical of a n-pentane where C1, C2, C3 and C5 are optionally substituted with OH, and M is optionally linked to a carrier protein.

attached to certain cyclophosphamide metabolites (e.g., 4-hydroxycyclophosphamide or aldophosphamide) prevents their enzymatic and chemical breakdown to cytotoxic products. An appropriate protein catalyst, conjugated to a tumor-selective reagent, is administered prior to the prodrug-, the catalyst thereupon produces active alkylating species in the vicinity of. . .

0  
CARRIER PROTEIN ]N N O2H  
\\J

Prodrugs of Other Antineoplastic Agents  
Prodrugs of a wide variety of antineoplastic agents are prepared by their conjugation to prodrug substituents of the invention. Ester or glycosyl substituents of the invention are appropriate for drugs with hydroxyl groups; amide substituents. . .  
hydrolyzes acetals (or ortho esters) to aldehydes

Alkenyl-glycerophosphocholine hydrolase (E.C. 3 2.2)

Cellulase (E.C. 3 1.4)

Oligo-1, 6-glucosidase (E.C. 3 1.10)

Lysozyme (E.C. 3 1.17)

P-D-Glucuronidase (E.C. 3 1.31)

D. Glycosidase - cleaves sugar substituents attached to drugs via an ether linkage

Examples include beta-galactosidases, beta-glucosidases, inulases, alpha-L-arabinofuranosidases, agarases, and isomerases. Specific examples include.

glycoprotein Goldrosen, M, et al.,  
hepatic metastasis Cancer Research 50  
(1990) 7978

It

Adenocarcinoma GI tract and other F023C5 Camino-embryonic Siccariello A.,  
Cancer

tissues antigen (CEA) Research 50 2-  
(1990):899s-903s

Carcinoma Head/Neck and E48 Peptide epitope within Gerretsen, M., et al.,

Vulva 22kD surface antigen British Journal of Cancer  
63 (1991):37-44

Carcinoma Larynx, pharynx CEA Kairemo, K., et al., A= and parotid gland Oncology 29  
(1990):539-543

Carcinoma Liver NP-4 CEA Wang, Z., et al., Cancer  
Research 0  
(1990):869s-872s

Carcinoma Breast CEA Kairemo, K., et al., A= Oncologic 29  
(1990):533-538

Carcinoma Bladder BW 431/26 CEA Boeckmann, W., et al.,  
British Journal of Cancer  
62 (1990):81-84

Carcinoma Ovary HWGI Milk fat globule glyco- Hird, V., et al., British  
protein (>200M).

of Cancer 63 (1991):37-44). Successful imaging has been possible even in patients with significant serum concentration of antigens shed from the tumor (CEA, Boeckmann, W., et al., British Journal of Cancer 62 (1990):81-84).

Chaudhary, et al., Proc. Natl. Acad. Sci. USA 84 (1987):4538-4542; Kondo J., et al.,

Biol. Chem. 263 (1988):9470-9475). Generation of analogous fusions using the growth

factors interleukin 6, interleukin 2, transforming growth factor alpha, and others are made by

linking enzymes or abzymes using the methods described in the above references. The

incorporation of catalytic antibodies into these is done via the fusion of these growth factors

to the end of antibody single chain gene constructs (Patent Application WO 88/01649) or

alternatively the growth factors.

The use of human CD4-Pseudomonas exotoxin fusion has proved effective in the killing of

HIV infected cells. The use of such a binding activity from CD4 linked to an enzyme or

catalytic antibody allows the use of prodrug therapy directed at

treatment of AIDS. The CD4 binds to the gp120 expressed on FHVI infected cells. The converse of such a construct makes use of gp120-enzyme (or catalytic antibody) fusion to develop an immunosuppression reagent system (Moore et al., Science 250, (1990):1139). Other g species which are useable in the subject invention. . .

#### Production of Bispecific Prg=iU

##### a. Production of Bispecific Proteins by Chemical Linkage of Enzymes or Catalytic

###### Antibodies to Targeting Proteins

The enzymes of this invention can be covalently bound to the targeting proteins of this invention by techniques well known in the art such as the use of the heterobifunctional cross-

linking reagents SPDP (N-succinimidyl-3(2-pyridyldithio)propionate) or SMCC (succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate [see., e.g., Thorpe, P. E., et al., The Preparation and Cytotoxic Properties of Antibody-Toxin Conjugates.

Immunological Rev., 62 (1982):119-58; Lambert, J. M., et al., supra at p. 12038;

Rowland, G. F., et al., supra, at pp. 183-84 and Gallego, . . .

##### b. Production of Bispecific Proteins by Recombinant DNA

Fusion proteins comprising at least the antigen binding region of the targeting protein of the invention linked to at least a functionally active portion of an enzyme or catalytic antibody of the invention can be constructed using recombinant DNA techniques well known in the art [see, e.g., Neuberger, M. S., et al., Nature 312, (1984):604-608]. These fusion proteins act in essentially the same manner as the antibody-enzyme conjugates described herein.

required enzymatic activity follows these basic procedures. To achieve the

optimized level of enzyme activity, manipulation of the sequences between the antibody and

enzyme may be needed. Addition of linker sequences

and/or alteration of the fusion site may

be needed for this optimization. In addition, to the advantage of a defined antibody-enzyme

reagent, the reduced size possible by the removal of the CH2 CH3, and the CH4 in the case of

IgE and IgM. . .

Methods for generation of bispecific antibodies consist of chemical methods of separation and

recombination of the antibody chains or by the fusion of the two hybridomas to generate so

called quadromas. These methods are effective but are prone to generate mixed species and require. . .

chain antibodies, in which the variable

(V) region of the two antibody chains are combined into a single molecule using a linker

sequence (Patent Application WO 88/01649, Ladner and Bird). This combination of V

regions results in expression of a protein which has one. . . of the V regions at the amino terminus and the other V region attached at its COOH terminus via the linker to its amino terminus. This head to tail, head to tail linkage of V regions has been described with both V light chain - V heavy chain and V heavy chain - V. . .

The construct would consist of the V Heavy chain region (VH) linked to the V Light chain region (VL); specific for the tumor cell or antigen via the linkers described for single chain antibodies (Vijay, et al., Nature 339 (1989):394-397; Patent Application WO 88/01649, Ladner and Bird); these sequences are linked directly to the catalytic antibody VL which can also follow VL-VH-VH-VL or VL-VH-VL-VH or VH-VL-VH-VL sequences. The linker sequences used in these constructions are those described above for single chain antibody construction. This combination allows the expression of a . . . species based on similar construction describes a previously unknown molecule as follows. The VH region specific for the tumor or antigen linked directly to the VL region of the catalytic antibody; this molecule is advantageously expressed separately or together with the other construct of VL specific for the tumor or antigen linked directly to the VH of the catalytic antibody. The expression products of these two molecules together, or by post expression mixing, associate. . . a lower molecular weight. The use of single domain binding proteins is also valuable to explore in the form of direct fusions to enzymes or catalytic antibodies (Patent Application WO 90/05144, Winter).

antibody expression library. In this system, rather than having the VH and VL genes as separate transcription units, they are covalently linked by a short peptide to produce a single chain antibody as defined by Bird, E., et al., Science 242 (1988) 426). Using. . .

use in this selection would include those haptens described herein. These antigens used for the raising of antibodies can also be coupled indirectly to a solid phase, such as epoxy activated Sepharose CL-6B, via coupling to a protein carrier. The choice of carrier protein is made such that the protein used for immunization would not be. . .

the cell wall of a P-lactamase enzyme-deficient E. coli causing death or impaired growth. In addition, these substituents optionally are used in coupling a carrier protein (KLH or BSA) during immunization.

portion may abolish or diminish the antibiotic action of aztreonam on E. coli. Screening with aztreonam rather than with the larger aztreonam-drug conjugate is acceptable because the antibodies are raised to a hapten that included the drug or an analog thereof and mutant antibodies. . .

Detection of prodrug activation is carried out by colorimetric or fluorometric determination of



the generation of galactose, which accompanies prodrug activation.

One of a number of possible galactose detection methods is employed. Some sensitive and specific detection methods follow-

I . Radiolabeling of free galactose with N<sub>E</sub>]ph]ha

a) Galactokinase (E.C. 2.1.6) is commercially available (Sigma Chemical Co., St.

Louis, USA) and catalyzes the following reaction;

galactose + ATP -->P- galactose-1-phosphate + ADP

If the ATP (adenosine triphosphate) used has <sup>32</sup>p in the gamma phosphate position, free

galactose generated by catalytic antibodies becomes radioactively-labelled. Labelled

galactose-1-phosphate is separated from the other constituents in the reaction mixture by thin

layer chromatography (TLC) or high performance liquid chromatography.

In this type of detection method, galactose is

non-catalytically reacted with commercially

available (from, for example, Molecular Probes, Inc., Eugene, OR)

aldehyde-reactive

reagents to yield a colored or fluorescent derivative. The product of the reaction with

galactose is isolated by HPLC or by TLC and detected by absorbance or by fluorescence by standard means.

Detection of galactose with color-generating specific enzymes.

a) One enzyme that can be used to detect galactose is galactose dehydrogenase (E.C.

1.1.8) (Sigma Chemical Company, St. Louis, MO, USA) which catalyzes the following oxidation-reduction reaction;

galactose + NAD<sup>+</sup> (no color) --> galactonate + NADH (color) + H<sup>+</sup>

The oxidation of galactose is accompanied by the reduction of nicotinamide adenine

dinucleotide (NAD<sup>+</sup>). The reduced form of NAD<sup>+</sup>, NADH, is colored and its appearance.

We

b) An alternative enzyme that is useful in detecting galactose is galactose oxidase,

(E.C. 1.3.9) which, used in combination with peroxidase and o-tolidine, will

cause a color change in response to the presence of free galactose generated by a

catalytic antibody. The coupled reactions are as follows. The first reaction is

catalyzed by galactose oxidase and the second by peroxidase, both available from

Sigma Chem. Company;

1. galactose + O<sub>2</sub> --> galactonate + H<sub>2</sub>O<sub>2</sub>

2.

H<sub>2</sub>O<sub>2</sub> + o-tolidine + H<sub>2</sub>O + colored product

The colored product generated can be measured spectrophotometrically.

A third method for in vitro detection of hydrolysis of aromatic ester nucleoside analogs is to

use an enzyme-linked assay. One inexpensive commercially-available enzyme (Sigma Chemical Company, St. Louis, MO) that could be used for this purpose is thymidine phosphorylase (E.C. 2.2.4). This enzyme converts the substrates thymidine and orthophosphate to the products thymine and 2-deoxy-D-ribose-1-phosphate. Rather than the prodrug being screened here, a conjugate of the inactivating ester with thymidine will be used (the same types of compounds that will be used in biological screening).

c) A third possible enzyme-coupled detection method employs both alcohol oxidase (E.C. 1.3.13) and peroxidase (E.C. 1.1.7). Alcohol oxidase can convert an aldehyde to a . . .

wherein a mammalian host is treated in a pharmaceutically acceptable manner with a pharmaceutically effective amount of a targeting protein catalytic protein conjugate or conjugates or bispecific antibody or antibodies and a pharmaceutically effective amount of a prodrug or prodrugs. The combination and methods of this invention. . .

target and localize at the tumor site. Such sufficient time may range from 4 hours to one week depending upon the conjugate used. The period of time between the end of administration of the immunoconjugate and the beginning of administration of prodrug varies depending. . .

or infusible solutions. The preferred form depends upon the mode of administration and the therapeutic application. For example, oral administration of the antibody-enzyme conjugate or bispecific antibody may be disfavored because the conjugate proteins tend to be degraded in the stomach if taken orally, e.g., in tablet form.

Another embodiment of this invention of this invention provides a method of combination chemotherapy using several prodrugs and only a single antibody-enzyme conjugate.

of prodrugs are used that are all substrates for the same enzyme or catalytic antibody in an immunoconjugate. Thus, a particular antibody-enzyme conjugate or bispecific antibody converts a number of prodrugs into cytotoxic form, resulting in increased antitumor activity at the tumor site.

and one wants to be certain that sufficient enzyme is targeted to the tumor site. The use of a number of conjugates bearing different antigenic specificities for the tumor increases the likelihood of obtaining sufficient enzyme at the tumor site for conversion of a . . .

(2 x 20 mL) in water ( 20 mL). The organic layer was separated, dried, concentrated, and flash chromatographed to afford the coupled compound as an oily material (0.66 g, 95 %, R<sub>f</sub>, 0.46, silica, methylene chloride, methanol, hexane, 80, 1, 19).

were protected to give iodide 3c. 3-Butyne-1-ol was transformed in four steps to alkyne 3d. Alkyne 3d and iodide 3c are

coupled using a Pd(II) catalyst to give nucleoside analog 3e (Robins, J. J., et al., J. Org.

2a, which is reacted with alcohol M to give diester 3g. Reduction and basic hydrolysis gives hapten 4, which can be linked to a carrier protein via the primary amino group.

dihydroxy compound 2c. Compound 2c, on treatment with PCI<sub>5</sub> in chloroform at 5°C afforded the phosphochloridate 2d. Compound M was coupled with phosphochloridate 2d in methylene chloride in the presence of DMAP to afford coupled compound 3h. Compound 3h was hydrogenated using Pd-C in ethyl acetate to afford the debenzylated compound which on treatment with aqueous ammonia.

Subsequent coupling with P-galactose pentacetate in the presence of trimethylsilyl trifluoromethanesulfonate in acetonitrile yielded the partially protected compound 17.

Coupling

Reaction- Coupling of Compound 17

To a solution of galactose penta acetate (1.17 g, 3 mmol ) and compound 16 (2 mmol) in dry acetonitrile (5 mL), a solution of trimethylsilyl.

21. Deprotection

of the silyl group was achieved using p toluene sulphonic acid at 0°C, and the resultant

product 22 was coupled with P-galactose pentacetate

in the presence of trimethylsilyl

trifluoromethanesulfonate in acetonitrile to give the fully protected compound 23. Complete

deprotection with ammonia in methanol.

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 170.34, 170.08, 157.56, 149.55, 139.17, 86.61, 83.72, 73.21

71.48, 61.65, 20.65, 20

Preparation of coupling compound 23: Coupling

reaction between galactose penta acetate

and compound 22 was accomplished by the method as mentioned above to give coupling

product 23 (R<sub>f</sub>, 0.20, 1:1 EtOAc: Hexane, 59%).

an amine which is then deprotected with

sodium methoxide in methanol to give the aminonucleoside 25. This aminonucleoside is

used in subsequent coupling reactions to give the amidine

compound 30b (R=5-fluorouridine).

Inversion of the

secondary hydroxy group using the Mitsunobu reaction procedure gives the galactolactam 29b derivative. Activation with Meerweins reagent and subsequent coupling with the amino nucleoside 25 (Example 5a) followed by desilylation with fluoride gives the final amidine compound 30b (R= 5-fluorouridine).

Preparation of the galactose-P fluorouridine amidine using 5-fluorouridine starts with commercially available glucopyranose 31. Treatment with 2,2 dimethoxypropane in acetone in the presence of catalytic amount. . . dimethylchlorosilane yields the glucolactarn compound 29a. The secondary hydroxy group is inverted using the Mitsunobu reaction procedure and the subsequent activation and coupling of the amide is accomplished using Meerweins reagent and the arminonucleoside 25 (Example 5a) respectively. Final deprotection using fluoride yields the.

enol phosphonate 56. Deprotection and reaction with phosphorus oxychloride, followed by N-trifluoroacetyl piperazine and then ammonia gives the hapten 57, which can be linked to a carrier protein through the piperazine ring.

To test if the prodrug could be activated by P-glact-oxidase, the enzyme was conjugated to an antibody that was directed against Carcino Embryonic Antigen (CEA) a specific tumor antigen on the surface of the LoVo culture cells. The Colo 320 DM cells lack this surface antigen and were used as controls. The P-galactosidase conjugated antibody was added to the cultures and allowed to bind the antigen. The prodrug, at different concentrations, was then added to the.

Figure 11 displays the results of this experiment which shows that the prodrug can be activated by the antibody-enzyme conjugate. By comparing Figure 11 with Figure 12, it is clear that the prodrug was not only activated by the conjugated antibody but also that the LoVo cells, carrying the CEA tumor marker are specifically killed when compared to the cultures where BSA was added with prodrug. The above results show that.

To assess the ability of surface-bound conjugate to generate cytotoxic levels of active drug, the rate of product formation was measured using ONPG as a substrate. Conjugate specifically bound to LoVo cells was found to generate  $1.2 \times 10^7$  molecules of product/min/cell. In our particular assay format, this rate.

be activated in vitro to produce levels of the drug similar to the pure drug itself. Thus, the addition of the galactose moiety onto the drug reduces the toxicity substantially and to a level that makes it an excellent candidate for a prodrug.

Galactosyl fluorouridine has been tested for targeted activation by P-galactosidase

conjugated to an antibody with the same CEA antigen tumor surface specificity as was done with the galAraC prodrug. The antibody was allowed to react with antigen-carrying cells (LoVo) and control cells without the CEA antigen marker. The prodrug was then added to different cultures at different concentrations.

Alcohol 74 undergoes a conjugate addition to ethynylsulfonate 75 to give the enol ether 76.

azido, and alkynyl groups gives amino alcohol 79, which is N-acylated and deprotected to give compound 81, which can be linked to a carrier protein at the primary aliphatic amino group.

However, the trifluoroacetate salt may be used for the reaction linking compound 81 at the primary aliphatic amino group to the carrier protein.

tissues. Fluorouridine is, however, toxic to normal tissues, particularly bone marrow and gastrointestinal epithelium. Prodrugs of fluorouridine that are activated by catalytic antibodies or enzymes targeted to tumor cells improve the therapeutic index of fluorouridine substantially. It is preferred that the prodrugs not be activated by endogenous.

C mice. This dose is far higher than would be administered in a therapeutic scenario involving targeted activation of fluorouridine prodrugs by anti-linked catalytic proteins.

mice to determine whether aldophosphamide diethyl acetal would in fact be relatively non-toxic and therefore suitable for targeted activation by an antibody-catalyst conjugate.

A linker moiety was first prepared, and then attached to the phosphorus of the hapten. The nitrogen of glycine was protected as the . . . The carboxyl group was then activated as the N-hydroxysuccinimide ester, forming compound 114, which was reacted with excess piperazine to form the linker moiety, compound 115.

to mice to determine whether aldophosphamide diethylacetal would in fact be relatively non-toxic, and therefore, suitable for targeted activation by an antibody-catalyst conjugate.

Arch. Allergy 121:21. Immunol. 94 (1991):11-20). The host immune response can be substantially reduced by conjugation of foreign proteins to, for example, copolymers of D-glutamic acid and D-lysine (D-GL), polyethylene glycols (PEG), monomethoxypolyethylene glycols (mPEG), or polyvinyl alcohols (PVA) (Sehon, A. H., Suppression of the IgE Antibody Responses with Tolerogenic Conjugates of Allergens

and Haptens, In Progress In  
AllerGX, Vol. 32 (1982):161-202). In each case, a protein such as an  
antibody (Ab) is  
modified with multiple molecules (n) of the conjugate; i.e.  
Ab(PEG)n. The suppression of  
the immune response depends on an optimum value of n; if n is too small  
or. . .

M., Sehon, A. H., Synthesis, Isolation, and Characterization of  
Conjugates of Ovalbumin  
with Monomethoxypolyethylene Glycol using Cyanuric Chloride as the  
Coupling Agent,  
Anal. Biochem. 165 (1987):114-127). The optimal value of n can be  
determined without  
undue experimentation by one skilled in the art. . .

Conjugation of a catalytic antibody or catalytic/tumor-binding  
bispecific antibody to  
nonantigenic molecules can be carried out as follows (Jackson, C. and J.  
C., Charlton, J. L.,  
ski, K., Lang, G. M., Sehon, A. H., Synthesis, Isolation, and  
Characterization of

Conjugates of Ovalbumin with Monomethoxypolyethylene Glycol  
using Cyanuric Chloride  
as the Coupling Agent, Anal. Biochem. 165 (1987):114-127). The  
optimum value of n (see  
above) is determined experimentally by one skilled in the art and the  
procedure can be varied  
to achieve this degree of conjugation. Preferably the antibody  
is conjugated to mPEG,  
although other conjugates may also provide the desired effect  
mPEG is preferred over PEG  
because PEG has two terminal hydroxyl groups which may participate in  
undesirable intra-  
and inter-molecular crosslinking of conjugates (Sehon, A. H.,  
Suppression of Antibody  
Responses by Chemically Modified Antigens, Int. Arch. Allergy Mpl.  
Immunol. 94  
(1991):11-20). The type of mPEG, . . . = 20,000) may also be chosen  
without undue  
experimentation. Additionally, the scale of the procedure is altered  
accordingly, depending  
on how much conjugated antibody is available or required.

2. The mPEG intermediate is reacted in the correct proportions with the  
antibody to  
form a conjugate with the desired value of n.

To obtain the antibody-mPEG conjugate (Ab(mPEG)) of varying n,  
different amounts of  
mPEG intermediate is added to 40 mg Ab. which is dissolved in sodium  
tetraborate. . .

Following conjugation, the mixture is passed through a  
Sephadex G-25 column (2.5 x 40  
cm) equilibrated with 25 mM Tris buffer, pH 8 The conjugates  
are finally purified on a  
DEAE-Trisacryl column (5 x 40 cm) pre-equilibrated in 25 mM Tris, pH 8  
The protein is  
bound. . . 5-Fluorouridine. The transition state analogue, the  
phosphonate ester of dimethoxy benzoyl fluorouridine compound 155 is  
prepared as  
described in Example 44. After conjugation of the phosphonate  
analogue to the carrier

protein, keyhole limpet hemocyanin it is used to immunize mice and to produce monoclonal antibodies. . . .

single chain antibody gene is then combined with a single chain gene for the catalytic antibody isolated as described above. The linking of these two single chain genes is in the form of the linkers already described for the combination of the single chains or other sequences known to be involved with the linkage of antibody domains; specifically genes coding for (ser-lys-ser-thr-ser)<sub>3</sub>, or hinge regions. These linked genes are then placed into an expression vector; in this instance, the vector pRC/CMS from In Vitrogen Inc., or other similar expression. . . .

CLMEN. . . . A compound having the formula:

R<sub>2</sub>'

R<sub>3</sub> R

R<sub>4</sub>

wherein X' is an analog of X of Claim 1, and Y is optionally linked to a carrier

protein,

B is O, S, NH, or CH<sub>2</sub>,

D is P(O)OH, SO<sub>2</sub>, CHOH or SO, if D is CHOH then B is CH<sub>2</sub>, and

RI', RTI RTJ R<sub>4</sub>' and R<sub>5</sub>' are the same or different, are optionally linked to a carrier

protein and are H, alkyl with I - I 0 carbon atoms, alkoxy with I - I 0.

11 A compound having the formula-

R<sub>6</sub>'

RT

Df, ], )B00000)C

R<sub>9</sub>'

wherein X' is an analog of X of Claim 7, and X' is optionally linked to carrier

protein,

B is O, S, NH, or CH<sub>2</sub>,

D'is P(O), COH, if D'is COH then B and Yare CH<sub>2</sub>,

Y' is O, . . . groups, ether groups, -CO-,

cyano, epoxide groups and heteroatoms.

R<sub>6</sub>'q R<sub>7</sub> t R<sub>8</sub>', and R<sub>9</sub>' are the same or different, are optionally linked to the carrier

protein and are H, alkyl with I - I 0 carbon atoms, alkoxy with I - I 0.

A compound having the formula:

R<sub>10</sub> t

RI' B\*#, %)C

R

wherein X' is an analog of X of Claim 13, and X is optionally linked to carrier

protein,

B is O, S, NH, or CH<sub>2</sub>,

D is P(O)OH, SO<sub>2</sub>, CHOH or SO, provided that if D is CHOH then B is CH<sub>2</sub>, and

R<sub>10</sub>'-IT which are optionally linked to the carrier protein, are the same or different but

at least two of them are not H, and are H. . . .

20 A compound having the formula:

R13 M]

14,

wherein X' is an analog of X of Claim 17, and X is optionally linked to a carrier protein,

B is O, S, NH, or CH<sub>2</sub>,

D is P(O), COH, provided that if D is COH, then B and Y are. . .

heteroatoms with 1-9

atoms in a linear configuration which have substituents that are phenyl, alkyl, or alkyl with

heteroatoms, and

R13'-14' which are optionally linked to a carrier protein are the same or different but at

least two of them are not H, and are H. . .

24 A compound having the formula:

R's

R17 R15'

IR18 x

wherein K is an analog of X of Claim 21, and X' is optionally linked to the carrier protein,

B is O, S, NH, or CH<sub>2</sub>,

D is P(O)OH, SO<sub>2</sub>, CHOH or SO, if D is CHOH then B is CH<sub>2</sub>, and R15'.) R16' R17', R18' and R19' are the same or different, are

optionally linked to the

carrier protein, and are H, alkyl with 1 - 10 carbon atoms, alkoxy with 1 - 10. . .

28 A compound having the formula:

FP'

R21

X

B O<sub>0e</sub>

wherein X' is an analog of the drug XNH<sub>2</sub> of Claim 25, and X' is optionally linked to

a carrier protein,

B is O1 S, NH, or CH<sub>2</sub>,

D is P(O), COH, provided that if D is COH then B and Y are. . . have substituents that are phenyl, alkyl, or alkyl with heteroatoms, and

R20', R21', R=, and R23' are the same or different, are optionally linked to the carrier

protein and are H, alkyl with 1-10 carbon atoms, alkoxy with 1-10 carbon atoms, monocyclic

aromatic, alkene with 1-10. . .

32 A compound having the formula:

D]eOBN\*%)C

wherein X is an analog of X of Claim 29, and K is optionally linked to the carrier

protein,

B is O, S, NH, or CH<sub>2</sub>, and

D is HP(O)OH, CH<sub>2</sub>OH, P(O)(OH)<sub>2</sub>, or SO<sub>3</sub>H, if D is CH<sub>2</sub>OH. . .

36 A compound having the formula:

RU

R26

R

wherein X' is an analog of X of Claim 33, and X' is optionally linked to the carrier

protein,

B is O, S, NH, or CH<sub>2</sub>,

D is P(O)OH, SO<sub>2</sub>, CHOH or SO, if D is CHOH then B is CH<sub>2</sub>, and



R24]-261 which are optionally linked to a carrier protein are the same or different and are H, alkyl with 2 to 22 carbon atoms, alkyl with. . .

A compound having the formula:

DI X

R2T B 000e

R28'

wherein X' is an analog of X of Claim 37, and Y is optionally linked to the carrier protein,

B is O, S, NH, or CH<sub>2</sub>,

D' is P(Q), COH, provided that if D' is COH then B and Y are heteroatoms with 1-9

atoms in a linear configuration which have substituents that are phenyl, alkyl, or alkyl with heteroatoms, and

R2T-28' which are optionally linked to the carrier protein are the same or different and

are H, alkyl with 2 to 22 carbon atoms, alkyl with. . .

least one of R30' and R3 V is an analog of X of Claim 41, and said analog

is optionally linked to a carrier protein,

D... is SO<sub>2</sub>, SO or CHOH, if D... is CHOH then Z is CH,

Z' is O, N, or CH; . . . or

acylamino with 1-10 carbon atoms with or without heterocyclic or phenyl substitution, and

R29' is optionally SO<sub>3</sub>H or SO<sub>4</sub>H, and

RN-33' are optionally linked to a carrier protein.

48 A compound having the formula:

R37 O

R36

B0000 X

R35' CH<sub>2</sub>)<sub>n</sub>

Al

wherein X is an analog of X of Claim 45, and is optionally linked to carrier protein,

B is O, S, NH, or CH<sub>2</sub>,

R34', R35%, R36% and R37' are the same or different and are H, . . .

compound having the formula:

O

(CH<sub>2</sub>)<sub>x</sub>

W

JAO]E1 B000'

R R43t

wherein X is an analog of X of Claim 49, and X' is optionally linked to carrier

protein,

B is O, S, NH, or CH<sub>2</sub>,

n is an interger from 0 to 4,

R43t and R4'V are the same. . .

E31

R46- NH QI- X

wherein Q' is O, S, NH, or CH<sub>2</sub>,

X is an analog of X of Claim 53, and X is optionally linked to a carrier protein,

B' is NH or CH<sub>2</sub>, if B' is NH, then Q' is CH<sub>2</sub>, and

R45' and R46' are the same or. . . different and are H. alkyl unsubstituted, alkyl

substituted with halogens, heteroatoms, phosphonate<sup>7</sup> sulfonate,

carboxylate,  
alkylammonium, alkene, or monocyclic aromatic, and are optionally  
linked to a carrier  
protein.

different and are H, alkyl unsubstituted, alkyl  
substituted with halogens, heteroatoms, phosphonate, sulfonate,  
carboxylate,  
alkylammonium, alkene, or monocyclic aromatic, and are optionally  
linked to a carrier  
protein.

X

wherein Q' is O, S, NH, or CH<sub>2</sub>,  
wherein X' is an analog of X of Claim 53, and X' is optionally  
linked to a carrier  
protein, and  
R<sub>45</sub>' and R<sub>46</sub>' are the same or different and are H, alkyl unsubstituted,  
alkyl  
substituted with halogens, heteroatoms, phosphonate, sulfonate,  
carboxylate,  
alkylammonium, alkene, or monocyclic aromatic, and are optionally  
linked to a carrier  
protein.

different and are H, alkyl unsubstituted, alkyl  
substituted with halogens, heteroatoms, phosphonate, sulfonate,  
carboxylate,  
alkylammonium, alkene, or monocyclic aromatic, and are optionally  
linked to a carrier  
protein.

63 A compound having the formula:

R<sub>47</sub>

NH

wherein X' is an analog of X of Claim 60, and which is optionally  
linked to a carrier  
protein,  
Q' is O, CH<sub>2</sub>, S, or NH, and  
R<sub>47</sub>' and R<sub>48</sub>' are the same or different and are H, alkyl unsubstituted,  
alkyl  
substituted with halogens, heteroatoms, phosphonate, sulfonate,  
carboxylate,  
alkylammonium, alkene, or monocyclic aromatic, and are optionally  
linked to a carrier  
protein.

different and are H, alkyl unsubstituted,  
alkyl substituted with halogens, heteroatoms, phosphonate, sulfonate,  
carboxylate,  
alkylammonium, alkene, or monocyclic aromatic, and are optionally  
linked to a carrier  
protein.

65 A compound having the formula-

R<sub>471</sub>

\1]

F141 NH

wherein X is an analog of X of Claim 60, and which is optionally  
linked to a carrier  
protein,  
Q' is CH<sub>2</sub>, and  
R<sub>47</sub>' and R<sub>48</sub>' are the same or different and are H, alkyl unsubstituted,  
alkyl

substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic, and are optionally linked to a carrier protein.

different and are H, alkyl unsubstituted, alkyl substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic, and are optionally linked to a carrier protein.

with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl ester or alkyl amide, hydroxyl, alkylammonium, amino, alkene, or monocyclic aromatic, and are optionally linked to a carrier protein.

having the formula:

ED

R511 NH

wherein Q' is O, S, NH or CH<sub>2</sub>,

X is an analog of X of Claim 17, and X is optionally linked to a carrier protein,

Vis NH or CH<sub>2</sub>, if B' is NH, then Q' is CH<sub>2</sub>, and

R50' and R51' are the same or. . . with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl ester or alkyl amide, hydroxyl, alkylammonium, amino, alkene, or monocyclic aromatic, and are optionally linked to a carrier protein.

the formula:

FtSD

R511 O1] x

wherein Q' is O, S, NH or CH<sub>2</sub>,

Y is an analog of X of Claim 67, and Y is optionally linked to a carrier protein, and

R50' and R51' are the same or different and are H, alkyl unsubstituted, alkyl

substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl ester or

alkyl amide, hydroxyl, alkylammonium, amino, alkene, or monocyclic aromatic, and are

optionally linked to a carrier protein.

with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl ester or

alkyl amide, hydroxyl, alkylammonium, amino, alkene, or monocyclic aromatic, and are

optionally linked to a carrier protein.

the formula:

'00e

G

NH a] X

wherein Q' is O, S, NH or CH<sub>2</sub>,

X' is an analog of X of Claim 75, and X is optionally linked to a carrier protein,

B' is NH or CH<sub>2</sub>, if B' is NH, then Q' is CH<sub>2</sub>, and

G' is a radical of the diol. . . cycloalkyldiol or ortho-phenyldiol, and G' is optionally substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic,

and is optionally  
linked to a carrier protein.

cycloalkyldiol or ortho-  
phenyldiol, and G' is optionally substituted with halogens, heteroatoms,  
phosphonate,  
sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic,  
and is optionally  
linked to a carrier protein.

compound having the formula:

G

a, -)C

wherein Q' is O, S, N-H or CH<sub>2</sub>,

Y is an analog of X of Claim 75, which is optionally linked to  
a carrier protein, and

G' is a radical of the diol G(OH)<sub>2</sub>, G(OH)<sub>2</sub> is a sugar, cycloalkyldiol or  
ortho-  
phenyldiol, and G' is optionally substituted with halogens, heteroatoms,  
phosphonate,  
sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic,  
and are optionally  
linked to a carrier protein.

cycloalkyldiol or ortho-  
phenyldiol, and G' is optionally substituted with halogens, heteroatoms,  
phosphonate,  
sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic,  
and are optionally  
linked to a carrier protein.

with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl  
ester or alkyl amide, hydroxyl, alkylammonium, amino, alkene, or  
monocyclic aromatic, and  
are optionally linked to a carrier protein.

87 A compound having the formula:

52,

\]-

R53 NH

wherein X' is an analog of X of Claim 82, and which is optionally  
linked to a carrier  
protein,

Q' is CH<sub>2</sub> or NH, and

R52' and R53' are the same or different, and are H, alkyl unsubstituted,  
alkyl

substituted. . . with halogens, heteroatoms, phosphonate, sulfonate,  
carboxylate or alkyl ester or  
alkyl an-dde, hydroxyl, alkylammonium, amino, alkene, or monocyclic  
aromatic, and are  
optionally linked to a carrier protein.

with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl  
ester or alkyl amide, hydroxyl, alkylammonium, amino, alkene, or  
monocyclic aromatic, and  
are optionally linked to a carrier protein.

89 A compound having the formula:

521

at X

R530

wherein X' is an analog of X of Claim 82, and which is optionally  
linked to a carrier  
protein,

Q' is CH<sub>2</sub>, and  
R<sub>52</sub>' and R<sub>53</sub>' are the same or different, and are H, alkyl unsubstituted, alkyl substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate or alkyl ester or alkyl amide, hydroxyl, alkylammonium, amino, alkene, or monocyclic aromatic, and are optionally linked to a carrier protein.

93 A compound having the formula:

00000

G'

NH

wherein Y is an analog of X of Claim 90, and which is optionally linked to a carrier protein,

Q' is CH<sub>2</sub> or NH, and

G' is a radical of the diol G(OH)<sub>2</sub>, G(OH)<sub>2</sub> is a sugar, cycloalkyldiol or ortho-

phenyldiol, and G' is optionally substituted with halogens, heteroatoms, phosphonate, sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic, and is optionally

linked to a carrier protein.

cycloalkyldiol or ortho-

phenyldiol, and G' is optionally substituted with halogens, heteroatoms, phosphonate,

sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic, and is optionally

linked to a carrier protein, and

R<sub>59</sub>' is H, alkyl unsubstituted, alkyl substituted with halogens, heteroatoms,

phosphonate, sulfonate, carboxylate or alkyl ester or alkyl amide, hydroxyl, alkylammonium,

amino, alkene, or monocyclic aromatic, and is optionally linked to a carrier protein.

95 A compound having the formula:

NH

wherein X is an analog of X of Claim 90, and which is optionally linked to a carrier protein,

Q' is CH<sub>2</sub>, and

G' is a radical of the diol G(OH)<sub>2</sub>, G(OH)<sub>2</sub> is a sugar, cycloalkyldiol or ortho-

phenyldiol, and G' is optionally substituted with halogens, heteroatoms, phosphonate,

sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic, and is optionally

linked to a carrier protein.

cycloalkyldiol or ortho-

phenyldiol, and G' is optionally substituted with halogens, heteroatoms, phosphonate,

sulfonate, carboxylate, alkylammonium, alkene, or monocyclic aromatic, and is optionally

linked to a carrier protein.

X is a radical of the drug XQH, where Q is O or NH, and

V is a hexopyranose or hexofuranose conjugated to QX via the anomeric position of the sugar with optional alpha or beta configuration.

nucleoside analog or phosphoran-dde

mustard [HOP(O)(NH<sub>2</sub>)N(CH<sub>2</sub>CH<sub>2</sub>CI)<sub>2</sub>], melphalan or doxorubicin.

100. A compound as in Claim - wherein V is Glucose, Glucosamine, D-Quinovopyranose,

Galactose, Galactosamine, L-Fucopyranose, L- Rhamnopyranose,

D-Glucopyranuronic acid,

D-Galactopyranuronic acid, D-manopyranuronic acid, or D-lodopyranuronic acid.

101. A compound having the formula:

N

z 01]x

M

wherein X is an analog of X of Claim 97, and which is optionally linked to a carrier

protein,

Q' is NH, and

M' is a 1,4-diradical of a n-pentane where C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub> and C<sub>5</sub> are optionally

substituted with OH, and M is optionally linked to a carrier protein.

102. A compound having the formula:

NH

/-]S

M' is a 1,4-diradical of a n-pentane where C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub> and C<sub>5</sub> are optionally

substituted with OH, and M' is optionally linked to a carrier protein.

103. A compound having the formula:

NH

I (t)]c

wherein X' is an analog of X of Claim 97, and which is optionally linked to a carrier

protein,

Q' is CH<sub>2</sub>, and

M' is a 1,4-diradical of a n-pentane where C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub> and C<sub>5</sub> are optionally

substituted with OH, and M' is optionally linked to a carrier protein.

104. A prodrug comprising a compound as claimed in Claim 1.

105. A pharmaceutical composition comprising:

(a) an effective. . . 2;

VL antibody I-S-VH antibody 1-S-VL antibody 2-S-VH antibody 2;

VL antibody I-S-VH antibody I-S-VH antibody 2-S-VL antibody 2;

wherein -S- is a linker sequence; and

(ii) isolating said bispecific antibody.

125. A method as in Claim 123 wherein antibody 1 is an antibody capable of. . . I -S-VL antibody 2,

(iii) combining the products of steps (i) and (h), and

(iv) isolating said bispecific antibody,

wherein -S- is a linker sequence.

127. A method of synthesizing a bispecific antibody comprising the steps of-

(i) expressing a gene having the sequence;

VL antibody 2-S-VH antibody 1, and

(ji) expressing a gene having the sequence:

VH antibody 2-S-VL antibody 1,

(iii) combining the products of steps (i) and (ii), and

(iv) isolating said bispecific antibody,

wherein -S- is a linker sequence.

128. A compound having the formula:

R 60o 0

N 11

R]Id CHCH<sub>2</sub>CH<sub>2</sub>O P(N(CH<sub>2</sub>CH<sub>2</sub>CI)<sub>2</sub>)<sub>2</sub>

wherein R<sub>60</sub> and R<sub>61</sub> are the same or different and independently. . .

substituted aromatic compound having the formula:

R67  
 R68 R66  
 N+oe A-  
 R B-X  
 wherein X is a radical of the drug XOH and is optionally linked  
 to a carrier protein;  
 B is O, S, NH or CH<sub>2</sub>;  
 D is HOP(O), SO<sub>2</sub>, CHOH or SO (with any stereochemistry);  
 R671 R689. . . or alkylammonium, and wherein  
 A- is an anion.  
 131. A therapeutic combination as recited in claim 111 wherein said  
 immunoconjugate  
 is modified by conjugation of a plurality of nonantigenic  
 molecules to the  
 immunoconjugate.  
 132. A therapeutic combination as recited in claim 112 wherein said  
 immunoconjugate  
 is modified by conjugation of a plurality of nonantigenic,  
 molecules to the  
 immunoconjugate.  
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	ENTRY	SESSION
FULL ESTIMATED COST	16.43	20.32

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=> s antibod?  
 L26 484149 ANTIBOD?

=> s enzyme?  
 L27 1013392 ENZYME?

=> s 126 (4W)127  
 L28 7572 L26 (4W)L27

=> s ?glucuronidase  
 L29 16687 ?GLUCURONIDASE

=> s 128 and 129  
L30 93 L28 AND L29

=> s CEA or (Carcinogenic Embryonic Antigen)  
6400 CEA  
195 CEAS  
6573 CEA  
(CEA OR CEAS)  
29571 CARCINOGENIC  
26 CARCINOGENICS  
29582 CARCINOGENIC  
(CARCINOGENIC OR CARCINOGENICS)  
79153 EMBRYONIC  
3 EMBRYONICS  
79154 EMBRYONIC  
(EMBRYONIC OR EMBRYONICS)  
306825 ANTIGEN  
244667 ANTIGENS  
387260 ANTIGEN  
(ANTIGEN OR ANTIGENS)  
3 CARCINOGENIC EMBRYONIC ANTIGEN  
(CARCINOGENIC(W) EMBRYONIC(W) ANTIGEN)  
L31 6574 CEA OR (CARCINOGENIC EMBRYONIC ANTIGEN)

=> s 131 and 130  
L32 7 L31 AND L30

=> d ibib 1-7

L32 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 1998:546530 CAPLUS  
DOCUMENT NUMBER: 129:254559  
TITLE: Prodrugs of anthracyclines for use in antibody  
-directed enzyme prodrug therapy  
AUTHOR(S): Florent, Jean-Claude; Dong, Xia; Gaudel, Gilbert;  
Mitaku, Sofia; Monneret, Claude; Gesson, Jean-Pierre;  
Jacquesy, Jean-Claude; Mondon, Martine; Renoux,  
Brigitte; Andrianomenjanahary, Solo; Michel, Sylvie;  
Koch, Michel; Tilleguin, Francois; Gerken, Manfred;  
Czech, Joerg; Straub, Rainer; Bosslet, Klaus  
CORPORATE SOURCE: Section Recherche, UMR 176 CNRS/Institut Curie, Paris,  
F-75248, Fr.  
SOURCE: Journal of Medicinal Chemistry (1998), 41(19),  
3572-3581  
CODEN: JMCMAR; ISSN: 0022-2623  
PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 1997:461628 CAPLUS  
DOCUMENT NUMBER: 127:104332  
TITLE: Cell-targeted cytotoxic drug therapy system, and  
preparation of associated compounds  
INVENTOR(S): Khan, Tariq  
PATENT ASSIGNEE(S): Aepact Limited, UK; Khan, Tariq  
SOURCE: PCT Int. Appl., 84 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:



PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9720580	A1	19970612	WO 1996-GB3000	19961206
W: CA, GB, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2239203	A1	19970612	CA 1996-2239203	19961206
EP 865298	A1	19980923	EP 1996-940685	19961206
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000502071	T	20000222	JP 1997-521082	19961206
PRIORITY APPLN. INFO.:			GB 1995-24942	A 19951206
			WO 1996-GB3000	W 19961206
OTHER SOURCE(S):		MARPAT 127:104332		

L32 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 1995:412729 CAPLUS  
 DOCUMENT NUMBER: 122:151369  
 TITLE: Modified glycosidation of fusion proteins of anti-tumor antibodies and prodrug activating enzymes and the use of the proteins in the targetted treatment of tumors  
 INVENTOR(S): Bosslet, Klaus; Czech, Joerg; Hoffmann, Dieter  
 PATENT ASSIGNEE(S): Behringwerke AG, Germany  
 SOURCE: Eur. Pat. Appl., 28 pp.  
 CODEN: EPXXDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 623352	A2	19941109	EP 1994-106394	19940425
EP 623352	A3	19950222		
EP 623352	B1	20020724		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
DE 4314556	A1	19941110	DE 1993-4314556	19930504
AT 220921	T	20020815	AT 1994-106394	19940425
ES 2177554	T3	20021216	ES 1994-106394	19940425
PT 623352	T	20021231	PT 1994-106394	19940425
AU 9461829	A	19941110	AU 1994-61829	19940502
AU 684750	B2	19980108		
CA 2122745	A1	19941105	CA 1994-2122745	19940503
JP 06319554	A	19941122	JP 1994-117524	19940506
US 2004202646	A1	20041014	US 2004-815925	20040402
PRIORITY APPLN. INFO.:			DE 1993-4314556	A 19930504
			EP 1994-106394	A 19940425
			US 1994-235395	B1 19940429
			US 1996-663406	B1 19960613
			US 1999-302434	B1 19990430

L32 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 1993:508496 CAPLUS  
 DOCUMENT NUMBER: 119:108496  
 TITLE: Molecular and functional characterization of a fusion protein suited for tumor specific prodrug activation  
 AUTHOR(S): Bosslet, K.; Czech, J.; Lorenz, P.; Sedlacek, H. H.; Schuermann, M.; Seemann, G.  
 CORPORATE SOURCE: Behring Res. Lab., Marburg, W-3550, Germany  
 SOURCE: Monoclonal Antibodies 2 (1993), 205-17. Editor(s): Epenetos, Agamemnon A. Chapman and Hall: London, Uk.  
 CODEN: 59CLAZ  
 DOCUMENT TYPE: Conference

LANGUAGE: English

L32 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1993:66829 CAPLUS

DOCUMENT NUMBER: 118:66829

TITLE: Fusion proteins of monoclonal antibodies and  $\beta$ -glucuronidase for site-specific prodrug activation

INVENTOR(S): Seemann, Gerhard; Bosslet, Klaus; Czech, Joerg; Kolar, Cenek; Hoffmann, Dieter; Sedlacek, Hans Harald

PATENT ASSIGNEE(S): Behringwerke A.-G., Germany

SOURCE: Eur. Pat. Appl., 34 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 501215	A2	19920902	EP 1992-102197	19920210
EP 501215	A3	19930811		
EP 501215	B1	20000524		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE				
DE 4106389	A1	19920903	DE 1991-4106389	19910228
AT 193326	T	20000615	AT 1992-102197	19920210
PT 501215	T	20001031	PT 1992-102197	19920210
ES 2149159	T3	20001101	ES 1992-102197	19920210
AU 9211251	A	19930128	AU 1992-11251	19920227
AU 660445	B2	19950629		
CA 2062047	A1	19920829	CA 1992-2062047	19920228
JP 07179500	A	19950718	JP 1992-78644	19920228
JP 3524933	B2	20040510		
GR 3033708	T3	20001031	GR 2000-401398	20000616
PRIORITY APPLN. INFO.:			DE 1991-4106389	A 19910228

L32 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1992:241811 CAPLUS

DOCUMENT NUMBER: 116:241811

TITLE: Molecular and functional characterization of a fusion protein suited for tumor specific prodrug activation

AUTHOR(S): Bosslet, K.; Czech, J.; Lorenz, P.; Sedlacek, H. H.; Schuermann, M.; Seemann, G.

CORPORATE SOURCE: Res. Lab., Behringwerke A.-G., Marburg, W-3550, Germany

SOURCE: British Journal of Cancer (1992), 65(2), 234-8

CODEN: BJCAAI; ISSN: 0007-0920

DOCUMENT TYPE: Journal

LANGUAGE: English

L32 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1991:605931 CAPLUS

DOCUMENT NUMBER: 115:205931

TITLE: Method for antibody targeting of diagnostic or therapeutic agents

INVENTOR(S): Hansen, Hans J.

PATENT ASSIGNEE(S): Immunomedics, Inc., USA

SOURCE: Can. Pat. Appl., 49 pp.

CODEN: CPXXEB

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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CA 2005162	A1	19910611	CA 1989-2005162	19891211
PRIORITY APPLN. INFO.:			CA 1989-2005162	19891211